Anti-IL-10/anti-PD-1 dual blockade leads to IFN-related HIV elite control signatures

Felipe ten-Caten[1], Khader Ghneim[1], Ana Carolina Santana[1], Muhamad Bilal Latif [1], Tamara Garcia[1], Perla Mariana Del Rio Estrada[1], Jeffrey D Lifson[2], Mihai Netea[3,4], Daniel M Gorman[5], Bonnie J Howell[5], Ashish Sharma[1], Mirko Paiardini[1,6], Hugo Soudeyns[1,7,8], Susan Pereira Ribeiro[1,9], Rafick P. Sekaly[1,9] & R37 study team

1- Pathology Advanced Translational Research Unit (PATRU), Department of Pathology and Laboratory Medicine, Emory University School of Medicine; 2- AIDS and Cancer Virus Program, Frederick National Laboratory for Cancer Research, Frederick, MD, USA; 3 - Department of Internal Medicine, Radboud University Medical Center; 4 - Center for Infectious Diseases, Radboud University Medical Center, Geert Grooteplein Zuid 8, 6525 GA Nijmegen, The Netherlands; 5- Department of Discovery Biologics, Merck & Co., Inc., South San Francisco, CA, USA; 6 - Division of Microbiology and Immunology, Emory National Primate Research Center, Emory University, Atlanta, GA, USA; 7 - Viral Immunopathology Unit, Centre de recherche Azrieli du CHU Sainte-Justine, Montreal, Canada; 8- Department of Microbiology, Infectiology & Immunology and Department of Pediatrics, Faculty of Medicine, Université de Montréal, Montreal, Canada; 9- Emory Vaccine Center, Atlanta, GA, USA;10Winship Cancer Institute of Emory University, Atlanta, GA, USA.

Introduction

Elimination of latently HIV-infected cells remain the biggest challenge to reach a cure. Current immunotherapy approaches have focused on targeting the adaptive arm of the immune system, such as therapeutic vaccines and the passive transfer of broadly neutralizing antibodies. Recent studies have shown that epigenetic reprogramming of innate myeloid cells triggered by adjuvants promoted protective interferon-induced antiviral immunity in vaccinees. We hypothesized that the dual blockade of IL10 and PD1 could synergize and lead to SIV-functional cure by triggering intrinsic antiviral immunity in monocytes and CD4 T cells resulting in lack of viral re-seeding post-ATI (Analytical Treatment Interruption) and by boosting innate and adaptive cellular effector function.

Dual Treatment leads to viral rebound control post-ATI and decay in viral reservoir

FIG 1

IL10 and PD1 dual blockade leads to SIV viremia rebound control for up to 6 months post-ATI

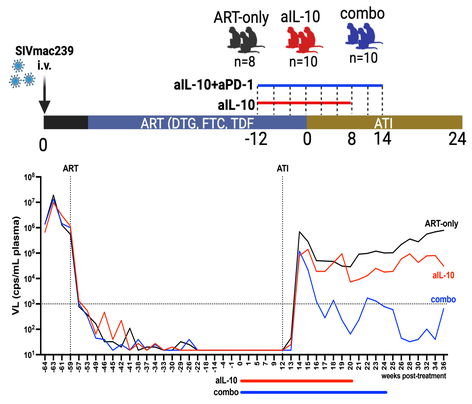
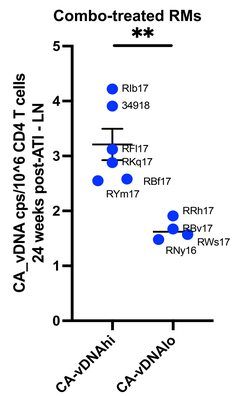
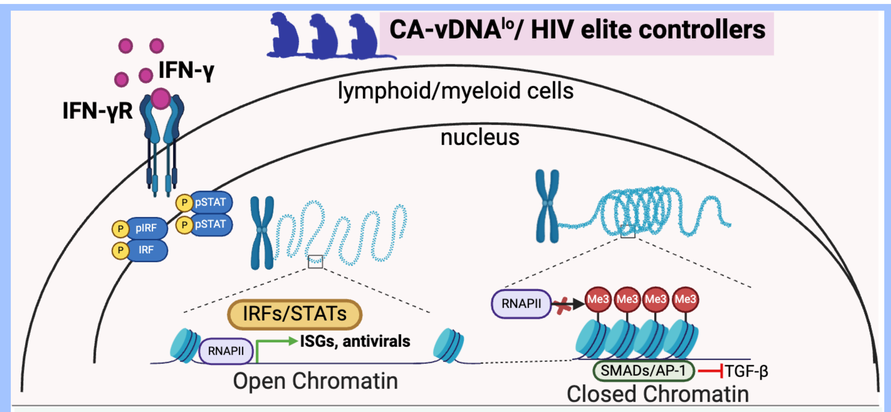
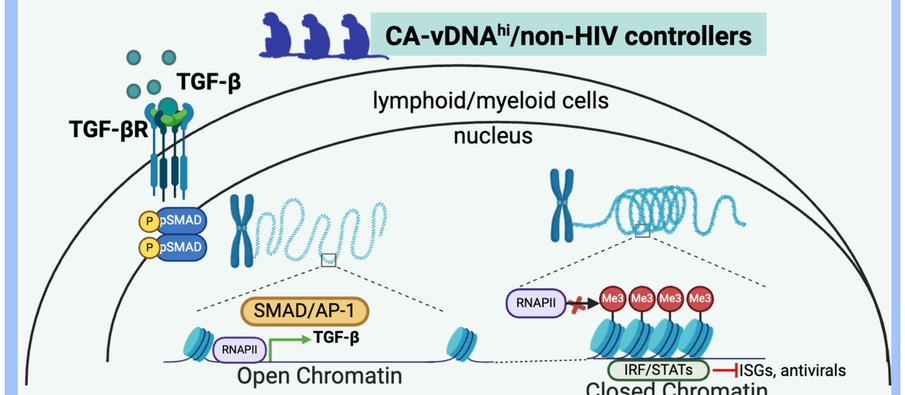


FIG 2

Dual therapy leads to significant reservoir decay in 40% of the treated animals







Methods

Twenty-eight rhesus macaques (RMs) were infected intravenously with SIVmac239. ART (TDF/FTC/DTG) was initiated at 42 days post-infection and maintained for 14-months prior to immune-therapeutic interventions. RMs received de-immunized aIL-10 (n=10), aIL-10/aPD-1 (n=10), or vehicle (n=8). ATI was performed 12-weeks after the first dose of therapy has started. Infusions continued for 14-weeks after ATI. RMs were followed longitudinally. Flow cytometry, cytokine array, and single-cell RNA-Seq/ATAC-Seq were conducted on SIV-infected, virologically suppressed rhesus macaques (RMs) treated with anti-IL-10 and anti-PD-1 antibodies (combo-treatment) before analytical treatment interruption (ATI).

FIG 3

Anti-viral ISGs are negatively correlated to virological outcomes at week 24 post-ATI

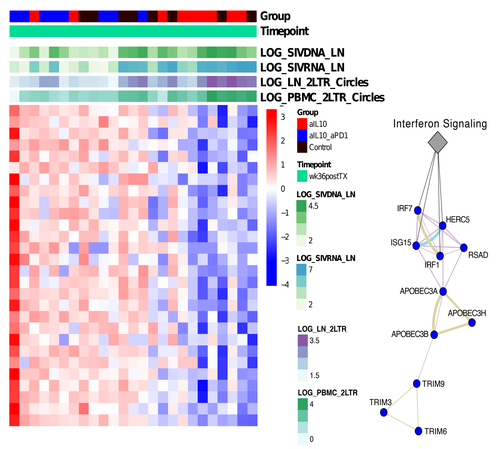


FIG 4

IL-6 and MIP-1α are elevated in CA-vDNA^lo RMs while TGF-β is decreased

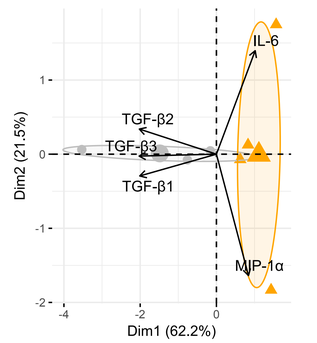
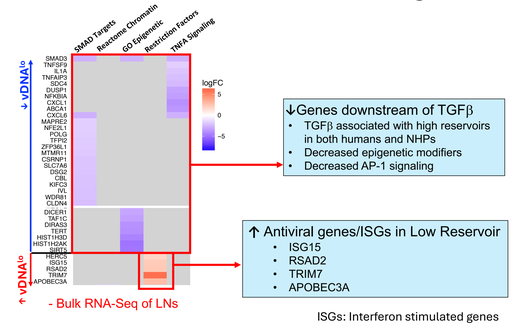


FIG 5

Antiviral signatures are elevated in CA-vDNA^lo and epigenetic modifications, SMAD2/3 targets and inflammation are downregulated



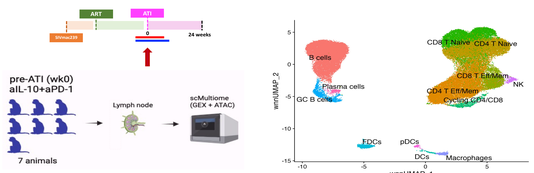
↓Genes downstream of TGFβ
- TGFβ associated with high reservoirs in both humans and NHPs
- Decreased epigenetic modifiers
- Decreased AP-1 signaling

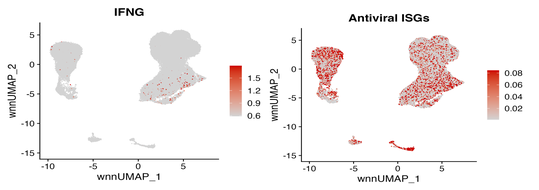
↑ Antiviral genes/ISGs in Low Reservoir
- ISG15
- RSAD2
- TRIM7
- APOBEC3A

ISGs: Interferon stimulated genes

FIG 6

Anti-viral ISGs are expressed across different immune subsets pre-ATI in lymph nodes from dual treated animals





scMultiome RNA-seq + ATAC-seq

FIG 7

Upregulation of IFNs and antivirals pathways and downregulation of inflammatory pathways in T cell subsets is associated to lower CA-vDNA in LNs post-ATI

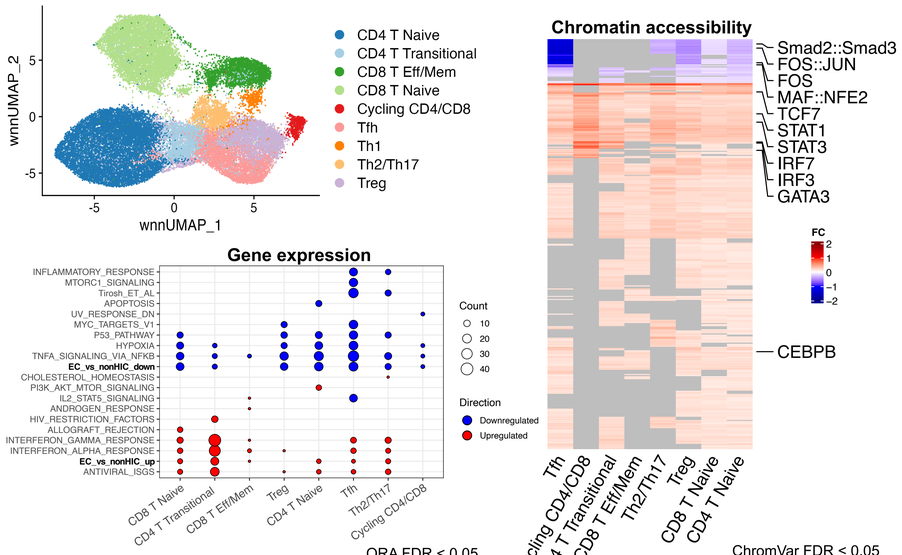


FIG 8

Protective signatures from combo-treated CA-vDNA^lo RMs overlaps signatures from HIV elite controllers

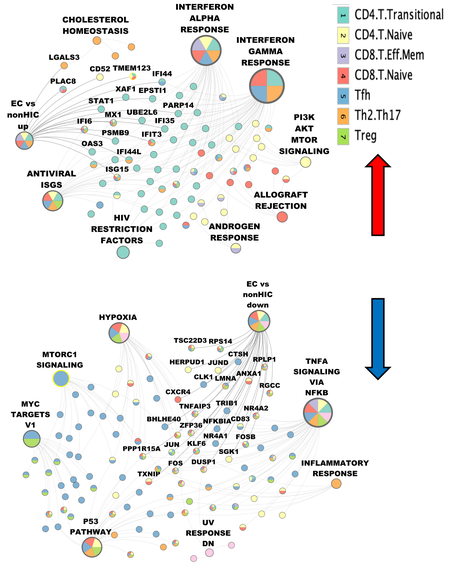
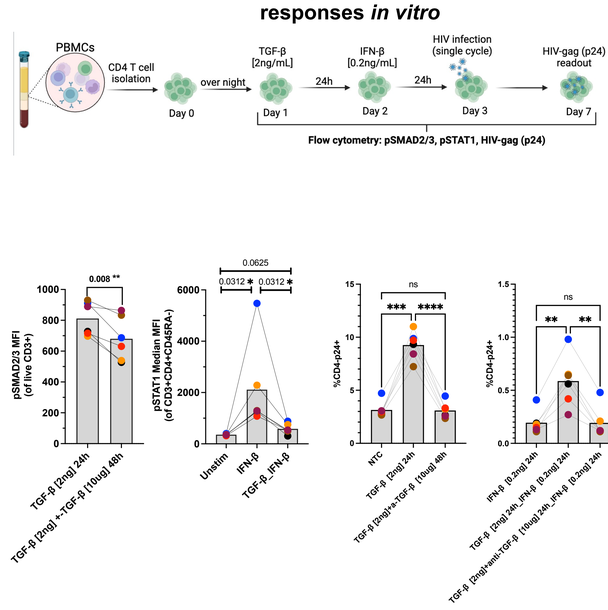


FIG 9

Stimulation with TGF-β blocks IFN-induced antiviral responses *in vitro*



Concluding Remarks

- RMs treated with aPD1+aIL10 controlled viral rebound post-ATI and had lower SIV-DNA in LNs
- Lower viral reservoir 24 weeks post-ATI is associated to pre-ATI: increased expression of antiviral ISGs, decreased inflammatory pathways, decreased plasma TGF-β levels
- This condition is associated to increased chromatin accessibility of IRFs and STATs binding sites and decreased FOS/JUN and SMAD2/3 target genes
- Same profile is observed in HIV ECs, who control viremia and present lower HIV reservoirs.

Financial Support

R37-AI141258
OD011132 (YNPRC)

ORIP/OD P51
CFAR – AI050409